POLYCYTHEMIA*

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INTRODUCTION AND CLASSIFICATION

POLYCYTHEMIA means an increase in red blood cells per unit volume of blood above a value which is considered normal. There are many causes for this state but whether the exact etiology is apparent in any given case or not, it is clear that the more knowledge we have about polycythemia, the more probable it is that all polycythemic states are either secondary or overcompensatory mechanisms to some general or local physiological or pathological change, rather than primary conditions.

While many classifications of polycythemia exist, probably the simplest is the division into two groups, suggested by Harrop and Wintrobe[1]—a mild type which might be called erythrocytosis, similar to leukocytosis; and the pronounced state or erythremia, analogous to leukemia. From a physiological viewpoint polycythemia may be (a) relative, as seen in conditions in which there is a loss of plasma; (b) transient, such as occurs after splenic contraction; and (c) absolute, when the total cell mass as well as the total blood volume shows a sustained and pronounced increase.

Erythrocytosis need concern us little in this discussion. It is seen in a variety of conditions and circumstances, such as congenital heart disease, mitral stenosis, pulmonary arteriosclerosis; at high altitudes; secondary to the action of many chemicals; and after hemorrhage.

Erythremia,[2] however, presents a distinct clinical picture and has been known by various names, as polycythemia vera, or polycythemia rubra. It is instructive in reviewing a disease to go back to original papers and see how much progress has really been made since a pathological concept was first described. In 1892 Vaquez[3] definitely claimed that polycythemia was due to hyperactivity of the hematopoietic organs, and

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in 1903 Osler[4] established all the cardinal evidences of this condition—cyanosis, polycythemia, and splenomegaly. It is also interesting to note that of his own four patients, one was a Russian Jew and one a Turkish Jew. In his 1908 paper[5] he suggested that anoxemia was the important pathological mechanism responsible for polyglobulism and mentioned the possibilities of x-ray therapy. These ideas are probably the most important features of polycythemia as we know it today.

Etiology

Many causes have been proposed to explain the etiology of erythremia. That a familial or hereditary type exists is generally accepted. The reports of Engelking[6] and of Spodaro and Forkner[7] give two excellent descriptions of this form. An outstanding feature of the familial, as contrasted with the ordinary type, is the fact that the individuals who have hereditary polycythemia rarely suffer from the severe symptoms of the disease. While an endocrine factor has been suggested because of the erythrocytosis in cases of pituitary basophilism,[8] hyperthyroidism, and suprarenal tumors, in most of these latter conditions the increase in erythrocytes rarely reaches the degree found in the ordinary type of polycythemia. Occasionally splenic tuberculosis and thrombosis of the splenic vein may also be characterized by an elevated red cell count, but these conditions are rare. A neoplastic conception of the cause of polycythemia is not generally accepted because of the absence of abnormal cells and the lack of invasiveness. A few reports[9,10,11] have been published of cerebral lesions inducing erythremia, such as injury to the proximal part of the vegetative brain centers, or diseases like encephalitis. Morris'[12] conception that polycythemia is due to excess secretion of a gastric substance, addisin, has not been verified by most workers.

This disease is most prevalent in males in middle or late life and there seems to be a preponderance among Jews born in Eastern Europe. This can be illustrated by a study of six institutions[13] in which the incidence of erythremia in this group was about 48 per cent contrasted with less than 10 per cent of general admissions. Such a finding naturally suggested an analogy to thromboangiitis obliterans and induced us to investigate the blood vessels of the bone marrow. It is important to make such studies on the bone marrow of subjects whose blood counts have approached normal by therapy to avoid excessive congestion of the bone marrow vessels which tends to make the vasculature scarce and, even in normal tissue,

Fig. 1—Artery in bone marrow of normal subject. Magnified × 280. Practically no fibrous tissue infiltration of wall of vessel.

Fig. 2—Artery in periosteum of arteriosclerotic patient. Magnified × 280. Fibrous tissue infiltrating muscularis.

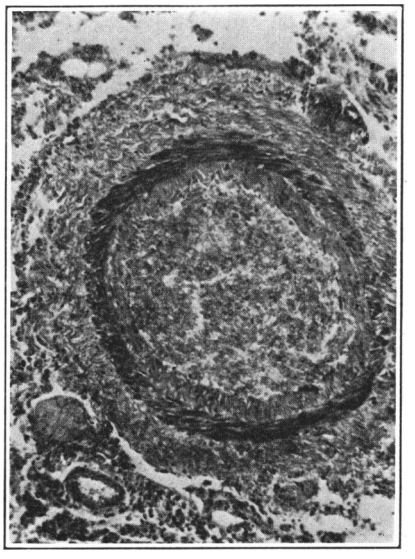

Fig. 3—Artery in bone marrow of a polycythemic patient. Magnified × 110. Marked fibrosis of subintima and adventitia.

TABLE I

RACIAL AND NATIONAL ORIGIN OF PATIENTS SUFFERING FROM POLYCYTHEMIA VERA

Institutions	*Total No. of patients (polycythemia vera)*	*Patients of Jewish origin born in eastern Europe (polycythemia vera)*		*General admission of patients of Jewish origin born in eastern Europe*
		No.	*Per cent*	*Per cent*
Bellevue Hospital	28	14	50	3 (sample year)
Cornell Clinic	7	4	57	12 (estimate)
New York Hospital...	19	12	63	9 (sample year)
Presbyterian Hospital.	33	13	39	15 (race not given; eastern European birth)
St. Luke's Hospital...	34	15	44	7 (race not given; eastern European birth)
New Haven Hospital..	13	6	46	10 (estimate)
	134	64	47.8	9 (approximate)

difficult to visualize. It is also essential to use a Masson trichrome stain to bring out the fibrous tissue adequately. Under such conditions it was found that in polycythemia the capillaries are markedly thickened and that in most cases the arteries and arterioles show adventitial and subintimal fibrosis. What causes such lesions is not known but it is of interest that in one early case the bone marrow showed inflammatory lesions along the course of the vessels. These observations have led us to propose the theory that erythremia may be due to local anoxemia in the bone marrow itself, with overcompensation of erythrogenesis. Since the lesion is local, the failure to lower the blood count by subjecting a patient to oxygen therapy is easily understood. Whatever the cause of polycythemia, all workers are agreed that the increase of erythrocytes in this condition is not due to decreased destruction or prolonged longevity of the red blood cells but is primarily dependent upon a heightened production.

PATHOLOGY

At autopsy the vessels are found to be engorged; hemorrhages and thromboses are common; the spleen and liver are large and hyperemic; and sometimes cirrhosis is seen. The marrow of the long bones is engorged and that of the short bones frequently is characterized by erythroblastosis and leukoblastosis. Increase of megakaryocytes is usual.

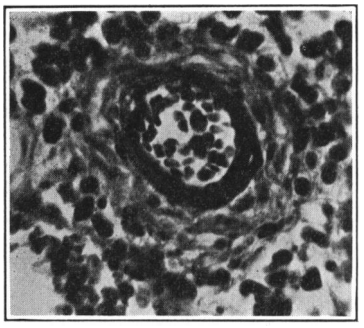

Fig. 4—Arteriole in bone marrow of normal subject. Magnified × 270. No fibrosis in wall of vessel.

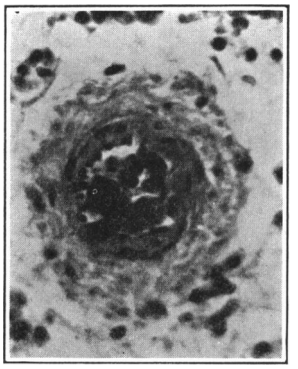

Fig. 5—Arteriole in bone marrow of polycythemic patient. Magnified × 540. Fibrous tissue infiltrating entire wall of vessel.

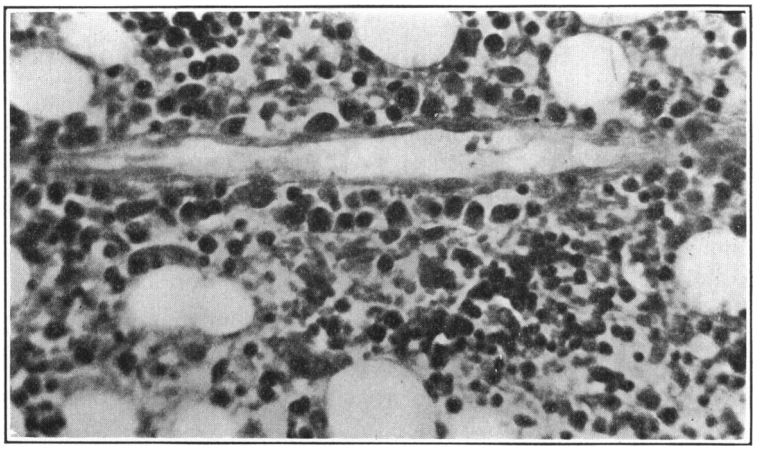

Fig. 6—Capillary in bone marrow of normal subject. Magnified × 270. Thin wall, nuclei bellying into lumen.

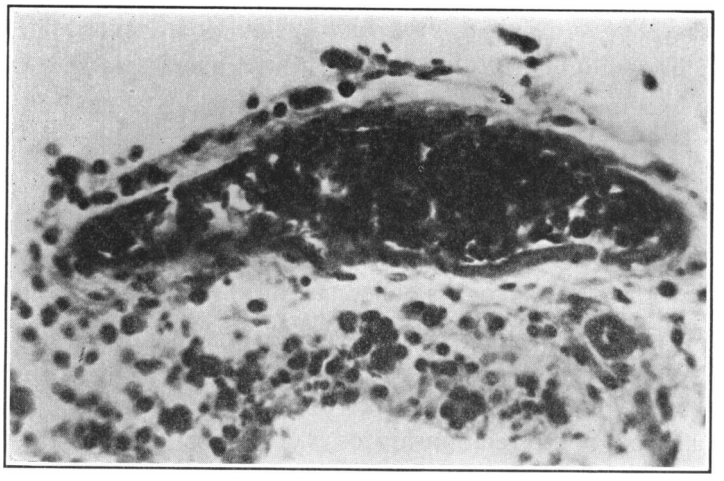

Fig. 7—Capillary in bone marrow of polycythemic patient. Magnified × 290. Marked thickening of wall. Cross section of markedly thickened small capillary in field.

Symptoms and Signs

The symptoms and signs of polycythemia are too well-known to require detailed description. The skin and mucous membranes show a cyanosis which is reddish blue, with dilated superficial vessels. Bleeding is not uncommon from the nose and gums, and these patients usually have bloodshot eyes. Erythromelalgia and skin eruptions occur occasionally. Clubbed fingers are usually absent in true polycythemia, but are seen in the familial type and in erythrocytosis secondary to heart and lung lesions.

Cardiovascular changes are common, especially arteriosclerosis, thrombosis, varicosities, and phlebitis. While true cardiac hypertrophy is rare, the x-ray picture usually shows some increase in heart size. Cardiac decompensation is a late phenomenon. Except for the Gaisböck type of polycythemia, which is really a nephrosclerosis, the blood pressure is only slightly elevated if at all.

Many of the symptoms of polycythemia are related to the nervous system. Usually patients complain of headache, dizziness, and a sense of fullness of the head. Paresthesias and pruritis are common. Vascular accidents in the fundi may cause blindness and the engorged tortuous vessels of the deeply colored retina explain the frequency of visual disturbances. Many complications involving the nervous system are due to the slowing of circulation of the cerebral vessels causing anoxemia.[14] While these occurrences may be transitory, actual thromboses and hemorrhages of the cerebral vessels may produce serious accidents. The average polycythemic patient is depressed and has a sluggish mentality. However, these individuals frequently demonstrate a combination of mental activity and irritability which makes them exceedingly uncomfortable household companions. It must be remembered that even when therapy has brought the blood count to normal, these nervous phenomena may persist and suggest that some of the disturbances are really due to vascular changes rather than to a polycythemia itself.

Many patients complain of pain and fullness in the left upper quadrant due to splenic enlargement, and constipation and flatulence are common. Gastrointestinal hemorrhages and thromboses produce a serious complication in erythremia. Cirrhosis of the liver may occur in the course of polycythemia and this lesion is explained on the basis of long continued congestion. One of the most interesting problems involving the gastrointestinal tract is the relationship of erythrocytosis to duodenal ulcer.[15]

Many of these patients do not have hyperacidity and although thrombosis of the vessels or erosion of distended vessels have been considered as causative factors, many workers now believe that the increase of erythrocytes, which is usually moderate, in many cases of duodenal ulcer is due to bone marrow overcompensation for low grade bleeding.

About three-fourths of all polycythemic patients have splenomegaly. This is not present in the Gaisböck type. The engorgement of the spleen may lead to infarcts and perisplenitis and cause severe pain.

Hirsch[16] has found nodules by x-ray examination of the lungs which he thinks may be subpleural thrombi or small hemorrhages. These disappear in about three weeks.

Laboratory Findings

The hematopoietic system has received much attention in this disease. The average red blood cell count in untreated patients varies between 8 and 12 million per c.mm., and the hemoglobin, which is normal in function, ranges between 18 and 24 gm. per 100 cc. of blood. The cells are usually normocytic, occasionally microcytic. Reticulocytes average between 1 and 2 per cent. Polychromatophilia, basophilic stippling, and even nucleated red blood cells may be found but the factor of hemorrhage or treatment by hemolytic agents must be considered when these immature forms are prevalent. Leukocytosis, polynucleosis, increase in immature polymorphonuclear cells, and thrombocytosis are usual. Tendency to hemorrhage is supposed to be due in part to poor clot retraction because of increase in cellular mass and decrease in serum. It is important, therefore, to undertake surgical procedures, such as dental extractions, with great care and to insist upon the hospitalization of the patient. The viscosity of the blood may be five to eight times normal and the specific gravity varies between 1.075 and 1.080, compared to the normal of 1.055 to 1.065. The sedimentation rate is greatly retarded. Haden[17] has recently emphasized the importance of determining the total red blood cell mass in diagnosing polycythemia. This is greatly increased since the total blood volume may be in some cases almost twice the normal; the hematocrit is markedly increased; and therefore the total cell mass may approach a three-fold rise.

Certain features concerning the hematological complications of polycythemia merit consideration. The relationship of this disease to leukemia has often been described and in fact some believe that there is a definite

disease entity known as erythroleukemia in which both diseases coexist. Others think that erythremia may terminate as a definite leukemia and still another group does not accept these concepts but holds that early in leukemia there may be an irritation of the contiguous erythrogenous bone marrow, giving an increase in red blood cell count. Whatever the true explanation of so-called erythroleukemia may be, it is not difficult to conceive of the contiguous irritation theory as one compatible with our knowledge of the bone marrow. Certainly the leukogenic and thrombocytogenic tissue shows evidence of stimulation in most cases of polycythemia, and this should afford no more surprise than does leukocytosis and thrombocytosis following acute hemorrhage.

Some polycythemic patients finally develop anemia and others thrombocytopenia with purpura. An exhaustion hypothesis has been proposed to explain these phenomena and this also fits in with the theory of the end result of prolonged anoxemia. However, it is important in such complications to be sure that one is not dealing with the final picture of prolonged depression therapy, either x-ray or chemical.

A few miscellaneous observations may be itemized. The basal metabolic rate may be increased. Whether this is due to increased formation of red blood cells or an increase in uric acid is not known. However, it is interesting to note that gout has frequently been reported complicating polycythemia.[18] The blood flow is slow, the skin capillaries distended, the respiratory minute volume is increased, and the vital capacity reduced. Albuminuria is usually present.

Therapy

It is not possible to review in detail all the methods which have been used to treat polycythemia. Therefore, this paper will deal principally with the four types of therapy used most commonly: venesection, acetylphenylhydrazine, irradiation, and Fowler's solution.

Venesection, removing 500 cc. of blood as often as twice a week, has in its favor the rapid amelioration of symptoms such as dizziness and headache. Recent work has shown that such a procedure produces very little bone marrow stimulation.[19]

Acetylphenylhydrazine, in doses of 0.1 gm. daily or every other day, until the blood count begins to fall and thereafter a maintenance dose, is well tolerated by most patients. This drug is not only hemolytic but apparently has some depressing action on the bone marrow. In using

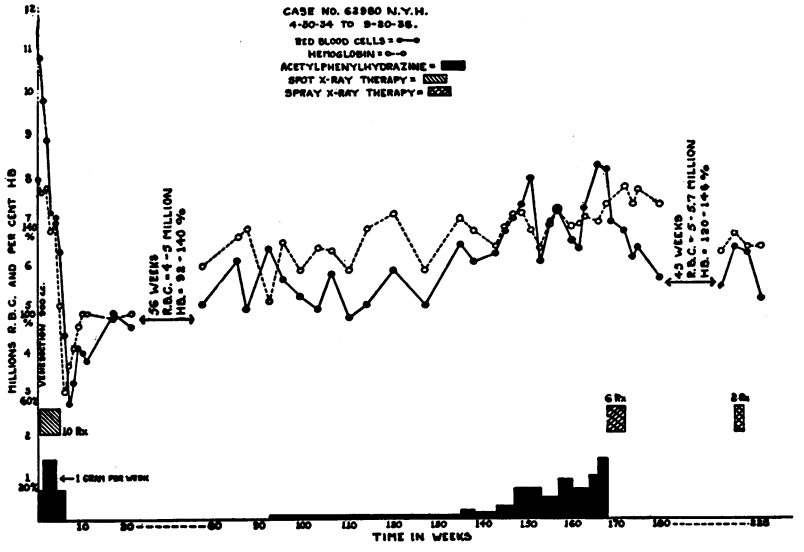

Fig. 8

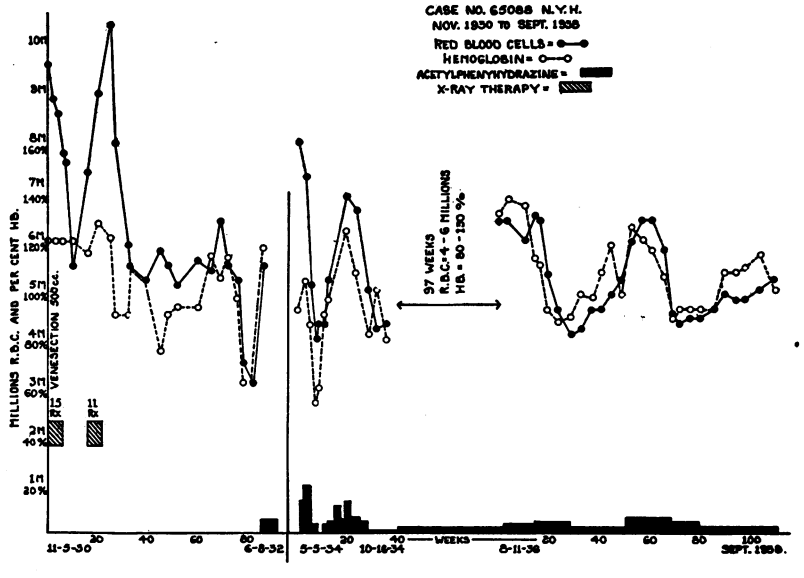

Fig. 9

Figs. 8, 9—Course of polycythemia treated with venesection, acetylphenylhydrazine and irradiation.

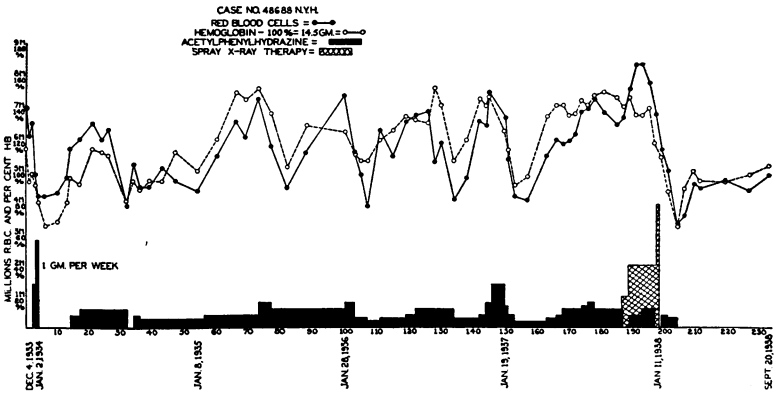

Fig. 10—Course of polycythemia treated with venesection, acetylphenylhydrazine and irradiation.

acetylphenylhydrazine it must be remembered that its action is cumulative and that patients vary markedly in their response to different doses. The incidence of thrombosis during the course of acetylphenylhydrazine therapy is probably no greater than can be explained by the disease itself.

Irradiation of the marrow and of the spleen has been used with success but recently many workers have claimed excellent results with spray radiation.[20] Figs. 8, 9, and 10 illustrate three cases in which these procedures were used.

Fowler's solution, prescribed according to Forkner's method,[21] is an effective drug in polycythemia and its successful use requires careful attention to detail.

Recently, normal propyl disulphide[22] has been suggested as a remedy in erythremia. It apparently has a phenylhydrazine-like action but has the disadvantage of giving the patient an onion odor.

The effectiveness of gastric lavage has not been substantiated nor is it practical.

Polycythemic patients, if properly treated, may have a long life, if not a merry one. It is important for the physician to pay attention to the emotional factors which may cause much unhappiness to the patient. As a general rule it is wise to avoid putting polycythemic patients to bed, since some activity is desirable in a disease complicated by thrombosis.

The diet should exclude condiments, too much roughage, alcohol, and foods and liquids which are very hot, as all of these may irritate the already congested gastrointestinal mucosa. Above all, it is important to keep the patient's blood count at a level which gives the greatest comfort and least complaint, rather than reach some arbitrary base line on a chart. The physician must not treat a blood count but the entire patient.

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